

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit : 1612
Examiner : Barbara P. Badio
Applicant : Verlan H. VanRheenen
Appln. No. : 10/815,351
Filed : April 1, 2004
Confirmation No. : 8270
For : CRYSTALLINE 19-NORSTEROIDS

REPLY BRIEF (37 CFR §41.41)

This Reply Brief addresses new points of argument raised in the Examiner's Answer and is intended to facilitate a proper resolution of the issues under appeal.

The main and perhaps the only issue that needs to be resolved is whether Appellant has provided sufficient evidence showing that the prior art did not enable the claimed compounds.

Appellant has expressly stated in the originally filed application that the base compound, 17 α -Acetoxy-21-methoxy-11 β -(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, was known and that crystalline pharmaceutically active compounds were known to be easier to work with, and therefore, more desirable than the corresponding free base. This is expressed at paragraph 0003 of the specification (page 1, lines 10-17). The applied prior art is relied upon for disclosing no more than what Appellant freely admitted at the time of filing.

Appellant's invention is an improvement over the known base compound, which exhibits great potential pharmaceutical utility, but has not been made available to the public because commercial use of the free base is impractical.

Appellant's invention also goes beyond the mere recognition that solid crystalline pharmaceutically active compounds are generally preferred over the corresponding free base.

Knowledge of a free base compound having great potential pharmaceutical utility coupled with knowledge that this potential utility can become a reality if the compound is provided in a solid crystalline form does not place the desired solid crystalline form of the compound in the possession of the person of ordinary skill in the art. The mere desirability for the invention does not make the invention itself obvious.

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It is beyond question that a claimed invention is not obvious in view of the prior art unless the prior art enables the person of ordinary skill in the art to make the invention. See *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) and *In Re Payne*, 606 F.2d 303, 314 (C.C.P.A. 1979).

Appellant has provided substantial evidence of non-obviousness in the Declaration of Verlan H. Van Rheenen (Exhibit 1 to the Appeal Brief filed January 14, 2009). This evidence shows that it was not known or obvious how to make the claimed salts and that only after numerous failures and considerable trial and error did Appellant discover an unorthodox technique for making the claimed salts.

Prior to the Appeal Brief, the Examiner did not place any weight on Appellant's evidence of non-obviousness, but instead argued that "[t]he issue is not the method of making the claimed salts but whether said salts would have been obvious to the skilled artisan" Thus, according to the Examiner, the mere fact that the hydrochloride and hydrobromide salts of steroids different from those of the claimed invention were known was sufficient to establish obviousness.

It appears that the Examiner now recognizes that the Final Rejection was inadequate because it did not properly address the legal requirement that the applied prior art in an obviousness rejection must enable the claimed invention. In an attempt to address this inadequacy, the Examiner's Answer now alleges "the conversion of pharmaceutical agents into a salt form is routine in the pharmaceutical art." According to the Examiner, unapplied prior art references (U.S. Patent No. 4,451,405, Examples 6-10; and U.S. Patent No. 3,723,524, Example L) disclose processes for making hydrochloride and hydrobromide salts of steroid compounds. The Examiner now further alleges that the processes disclosed in the unapplied '405 and '524 patents "are similar to that of the instant specification, i.e., reaction of the free base of the desired compound with the appropriate acid, for example, hydrochloric or hydrobromide [sic] acid." The Examiner also now states (Examiner's Answer at page 5, lines 3-6) that because of "the importance of salts of pharmaceutical agents and the FDA approval of hydrochloride and

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hydrobromide salts of pharmaceuticals, it is the examiner's position that the claimed salts are *prima facie* obvious."

The Examiner's allegations do not constitute evidence to be weighed against Appellant's evidence of non-obviousness. Further, given the unpredictability in the chemical arts, the mere fact that the prior art discloses different salts prepared using allegedly similar processes is not sufficient to establish *prima facie* obviousness. The person of ordinary skill in the art recognizes that each chemical species is unique, and that preparation of a corresponding hydrochloride or hydrobromide salt is not always possible, and when possible, may involve vastly different techniques. Regardless, Appellant has presented evidence showing that conventional techniques, such as those described in the unapplied '405 and '524 patent references relied upon in the Examiner's Answer will not lead to the claimed invention.

The allegation in the Examiner's Answer that the processes disclosed by the unapplied '405 and '524 patent references are similar to those used to make the claimed invention is an admission that there are differences. These differences have not been addressed. The unapplied '405 and '524 patents disclose simple addition of hydrochloric acid in water to the base or a suspension of the base in water to obtain the desired hydrochloride salt. There is no question that the primary Kim et al. reference (U.S. Patent Application Publication No. 2002/0025951) would have disclosed the claimed salts if they could have been prepared by simply adding hydrochloric acid to the free base form of the compound. Further, Appellant has presented evidence (the Declaration of Verlan H. Van Rheenen) expressly stating that several early attempts at preparing the claimed hydrochloride and hydrobromide salts were unsuccessful (paragraph 13 of the Declaration), and that it was only after these many unsuccessfully attempts that a successful unconventional technique was discovered. This technique did not involve the addition of hydrochloric acid or hydrobromic acid to the free base, but instead involved adding anhydrous hydrogen chloride in ether to the free base dissolved in ethyl acetate to yield an oil deposit. Appellant also discovered that the oil deposit could be re-dissolved in acetone and that upon addition of ethyl acetate and ether, an amorphous solid precipitate was formed. Upon stirring at

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40°C, the amorphous solid was slowly converted into the claimed white, crystalline solid (see paragraph 14 of the Declaration of Verlan H. Van Rheenen).

The Examiner's allegation regarding "knowledge of the skilled artisan as to the importance of salts of pharmaceutical agents" does not support *prima facie* obviousness. Rather, it is evidence of a long-felt, but unfulfilled need for the claimed compounds. Appellant did not file his application until April 4, 2003, almost seven years after the priority date of the Kim et al. reference disclosing the free base form of the claimed salt. Appellant's declaration also discloses the failure of others (Chiu Hong Lin) to make salts of the corresponding free base compound.

It is respectfully submitted that the evidence showing a long-felt, but unfulfilled need; the failure of others; and the unorthodox techniques employed for achieving the claimed invention constitutes substantial evidence overcoming the alleged showing of *prima facie* obviousness.

In the Examiner's Answer, a previously abandoned position regarding the law of *In Re Williams*, 89 USPQ 396 (CCPA 1951) was resurrected. The Examiner once again alleges that the court held that "salts of known compounds are *prima facie* obvious." As previously explained in a response dated November 2, 2007, the *Williams* court did not hold that salts of known compounds are *prima facie* obvious. Rather, the *Williams* court held that simple salts that are prepared by reacting an acid with an alkali metal hydroxide are obvious where the salt has no enhanced utility over the acid. The claims at issue are not directed to simple salts nor are they directed to a reaction product of an acid and an alkali metal hydroxide. Moreover, the claimed 19-norsteroid salts have considerably more utility than the base compound. This fact is confirmed by the Examiner, who repeatedly refers to the desirability and importance of providing solid crystalline salt forms of free base compounds. In the case of *In Re Williams*, the person of ordinary skill in the art was enabled. In other words, the person of ordinary skill in the art would have correctly predicted that a simple salt can be prepared by reacting an acid with an alkali metal hydroxide. However, the claimed invention is not enabled. The person of ordinary skill in the art could not have predicted, based on the teachings of the prior art, an appropriate technique for preparing the claimed salts.

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CONCLUSION

The weight of evidence on the record shows that the person of ordinary skill in the art would not have found enablement for the claimed invention in the applied prior art, or in the applied prior art combined with the unapplied prior art now relied upon by the Examiner (U.S. Patent Nos. 3,723,524 and 4,451,405), such that a reversal of the rejection is proper.

Respectfully submitted,

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Date

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